PETITION FOR EXTENSION OF TIME

Applicants petition for a three-month extension of time for response from January 1, 1994 up to and including April 1, 1994. A check in the amount of $840.00 for the required fee is enclosed. The Commissioner is authorized to charge any underpayment of the required fee to Deposit Account No. 23-1703.

REMARKS

Claims 1-3 and 5-13 are pending in the instant application.

Applicants acknowledge the Examiner's withdrawal of the rejections of the claims under 35 U.S.C. § § 101 and 112.

The Examiner has rejected claims 1-3 and 5-7 under 35 U.S.C. § 103 as obvious over U.S. Patents No. 3,983,233 to Brattsand et al. ("Brattsand") and No. 3,494,974 to Murakami et al. ("Murakami") in view of the acknowledgments on page 3 of the instant specification, i.e., (Ann. Allergy 63: 220-224, 1989 "Marsac"; Lung, 168, 105-110, 1990 "Svedmyr" ; EP 416950 and EP 416951). Applicants acknowledge that the Examiner asserts that Brattsand does not disclose or claim the use of corticoid compounds in compositions with other active ingredients such as β_2-adrenoreceptor agonists as is instantly claimed.

Applicants maintain that the Examiner is in error in asserting that the invention is obvious over Brattsand in combination with the teachings of the secondary references. Regarding Murakami, this reference does not teach or suggest the instant pharmaceutical compositions. Murakami discloses bronchodilating agents as active ingredients for administration as β-adrenergic stimulants of respiratory smooth muscle. As exemplified in Table III, Murakami's pharmaceutically active compounds are administered alone as salts of nontoxic acids. Applicants do not disagree that the compounds disclosed in Murakami are bronchodilating agents and that they can be administered as aerosols. However, the reference of Murakami fails to teach or suggest the present invention, which is the sequential or simultaneous administration of a combination of a bronchodilator in combination with an anti-inflammatory agent, or *vice versa* in the treatment of respiratory disorders.

As asserted by the Examiner, Applicants' invention differs from the references of Brattsand and Murakami in that the references fail to highlight the combined use of budesonide and formoterol for treating a respiratory condition such as asthma where the ingredients are administered in sequence or together in one composition. Applicants disagree with the Examiner's contention that it would have been obvious to the skilled artisan motivated by a reasonable expectation of success to reconcile the

differences between the references since the compounds share a common utility.

Applicants assert for several reasons that it would not have been obvious to a skilled artisan to combine compounds as in the present invention with the expectation of success merely because both compounds share the same utility.

First, compounds which exhibit different chemical and physical properties cannot necessarily be readily combined into a single formulation. That is, compounds such as budesonide, an anti-inflammatory steroid, and formoterol, an alcohol, not only have different kinetic properties, but they may be dissimilar regarding, *inter alia*, solubility, stability, absorption, distribution, excretion and interaction with other drugs.

Second, none of the references, either alone or in combination, disclose the combination therapy of the instantly claimed invention. In addition, there is no common principle in the art for fixed combinations of a steroid and a β-agonist in the treatment of asthma ("Fixed dose combination therapy in the treatment of asthma - the case against it", in: Mechanisms in Asthma, Pharmacology, Physiology and Management, pp. 421-425, 1988), and none of the prior art relating to combination therapy, such as the prior art disclosed on page 3 in Applicants' specification (Drug Ther. Bull. 24: 15-16, 1986; BMJ 288, Feb. 11, 1984; Drugs 24: 414-439, 1982), discloses or suggests the instant invention. Both Marsac and Svedmyr disclose the use of

steroid therapy and β-agonists in the treatment of asthma. However, contrary to the instant invention, in Marsac and in Svedmyr these compounds are administered separately. Thus, neither Marsac nor Svedmyr teach or suggest that a steroid and a β-agonist can be delivered together either simultaneously or sequentially in order to achieve successful therapy as is instantly claimed.

Positive effects in treating respiratory diseases such as asthma result in conscientious patient compliance, and although both EP 416950 and EP 416951 disclose combination therapies in the treatment of respiratory disease, e.g. salbutamol and beclomethasone dipropionate, they also disclose that such a combination "suffers a number of disadvantages in view of the...short duration of action exhibited by salbutamol" and thus "...may discourage effective patient compliance." Poor patient compliance or noncompliance with regimens of inhaled drugs in asthma has been shown to be a significant cause of asthma morbidity (see Resp. Med. 84: 61-66, 1990; Resp. Med. 84: 67-70, 1990, copies enclosed).

As disclosed in New Drugs in Allergy and Asthma, 253-269, 1993, although both salmeterol and formoterol are long-acting β-agonists, the latter exhibits faster onset of effect than does the former when clinical pharmacology profiles are compared, and thus formoterol has been shown to be a significantly better bronchodilator. Thus, regimens involving

the inventive compositions would be expected to enhance patient compliance.

An additional consideration is that short-term β-adrenoreceptor agonists such as salbutamol, in high doses, may yield deleterious effects which are life-threatening in long-term treatment of asthma, since there are indications that short-term β-agonists suppress the β-receptors, and thus they may not be suitable for long-term treatment. Glucocorticosteroids such as budesonide are believed to reactivate the β-receptors in this situation, and thus would not cause such problems.

The combination of budesonide and formoterol is not mentioned or taught by any of the cited references. Furthermore, many of the presently understood considerations indicating the superiority of the claimed compositions and methods of treatment employing the compositions were not known to those of ordinary skill in the art at the time of filing the instant application. It would not have been obvious to one of ordinary skill in the art nor would such an artisan have been motivated to make the instant compositions and to employ them in the instantly claimed methods of treatment, particularly in an art wherein fixed combination therapy employing these types of compounds has been regarded as not offering sufficient advantage to outweigh the considerable disadvantages associated with the ordinary clinical context. There would have been no reason for the skilled artisan to expect that the instant combination would be more advantageous

to use because, for example, they would effect enhanced patient compliance.

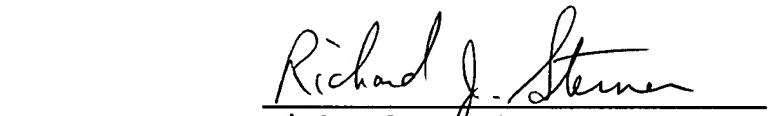
The argument projected by Examiner seems to be one of an "obvious to try" nature. Although it might be obvious to try combinations of prior art teachings, such evidence does not establish a *prima facie* case of obviousness absent some teaching, suggestion or motivation to combine. *In re Geiger* 231 USPQ2d 1276 (CACF 1986). It has long been settled that "obvious to try" is not a valid basis for rejection and such is contrary to statute. *In re Goodwin et al.* 198 USPQ 1 (CCPA 1978).

Based on the above, it is submitted that the application is in condition for allowance. Reconsideration and allowance of claims 1-3 and 5-13 are respectfully requested.

Any additional fees due in connection with this response should be charged to Deposit Account No. 23-1703.

Date: April 1, 1994

Respectfully submitted,



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Enclosures